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(54) Title: COMPOSITION AND METHOD FOR SUPPLEMENTING TESTOSTERONE IN WOMEN WITH SYMPTOMS OF TESTOSTERONE DEFICIENCY

(57) Abstract

The present invention provides compositions and methods for providing androgenic steroids, such as testosterone, in effective amounts to women who are in need of androgenic steroid supplementation.

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COMPOSITION AND METHOD FOR SUPPLEMENTING TESTOSTERONE IN WOMEN WITH SYMPTOMS OF TESTOSTERONE DEFICIENCY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of US Provisional Application No. 60/037,473, filed on February 7, 1997; US Provisional Application No. 60/039,717, filed February 12, 1997; and US Provisional Application No. 60/046,642, filed May 16, 1997.

BACKGROUND

Women who are menopausal, either naturally or as a result of ovarian failure or loss (e.g., secondary to hysterectomy, surgical oophorectomy or chemotherapy) frequently develop testosterone deficiency, with its attendant undesirable effects.

Because of the above, it would be desirable to provide compositions and methods for their administration that would enable women exhibiting symptoms of testosterone deficiency to take supplemental amounts of and androgenic steroid in such a manner as to restore physiological testosterone levels and promote the return of sexual health and activity, promote feelings of well-being, promote cardiovascular and coronary health, maximize muscle tone and inhibit bone loss. The present invention is drawn to the attaining of these desires.

SUMMARY OF THE INVENTION

The present invention relates to compositions and methods for providing androgenic steroids in effective amounts to women who are in need of supplementation, such as women whose total serum testosterone or free testosterone levels are less than optimal or significantly below normal physiological levels due to menopause and/or natural aging or as a result of hysterectomy or ovarian failure (e.g., consequent to chemotherapy), or adrenal insufficiency.

In one embodiment a topical formulation, comprising effective amounts of androgenic steroids in a pharmaceutically acceptable carrier, is applied to the genital mucosa for a period of time sufficient to overcome or ameliorate symptoms of testosterone deficiency.

The invention also relates to a method of progressively providing androgenic steroids in effective amounts to women who are in need of testosterone supplementation, by means of first applying to the genital mucosa effective amounts of androgenic steroids in a pharmaceutically acceptable carrier for a time sufficient to bring the testosterone level to within physiological ranges as determined by serum blood levels ("total testosterone") or serum free testosterone unbound to sex hormone binding globulin ("free testosterone"). Once the testosterone levels are within physiological ranges, the topical application to the genital mucosa is replaced by the oral, transdermal or parenteral administration of lower amounts of androgenic steroids to maintain the testosterone levels within the desired physiological ranges.

Obviously, the need for supplementing androgenic steroids should be determined by a physician or other health care professional based on monitoring symptoms of testosterone deficiency. Not every female will exhibit the same symptoms and it is possible that testosterone levels might even be within physiological ranges but, based on other factors, testosterone deficiency may still be diagnosed. Such symptoms might include, but not be limited to, global loss of sexual desire, decreased sensitivity to sexual stimulation in the nipples and in the clitoris, decreased arousability and capacity for orgasm, diminished vital energy and sense of well-being, and, loss of muscle tone. Some women also notice other symptoms such as thinning and loss of pubic hair, genital atrophy not responsive to estrogen, dry and

brittle scalp hair, and, dry skin. Other symptoms, while less documented, include cardiovascular and coronary heart disease and dry eye in patients suffering from Sjogren's syndrome.

It is therefore highly desirable, if not imperative, that testosterone supplementation for a female patient be based on a diagnosis by a physician who prescribes the mode of application, dosage and duration of treatment.

As noted in U.S. Patent 5,460,820, the transdermal administration of between about 50 to 500 µg of testosterone per day is usually sufficient to maintain serum blood levels of between about 15 to 80 ng/dl. On the other hand, the daily dosage of methyltestosterone, administered orally, is suggested to be between about 100 to 800 µg (i.e. 0.10 to 0.80 mg/day).

When used within the context of this invention, the terms "androgenic steroid", "testosterone agent" or "testosterone" (when used generically), must be taken in context and are generally meant to encompass any androgenic steroid that is functional in reducing symptoms of testosterone deficiency in females. Members selected from the group consisting of natural testosterone, testosterone esters, methyltestosterone, methyl testosterone esters, androstenedione, andrenosterone, dehydroepiandrosterone, fluoxymesterone, methandrostenolone, 17α-methylnortestosterone, norethandrolone, dehydrotestosterone, oxymetholone, stanozolol, ethylestrenol, oxandrolone, bolasterone and mesterolone are representative of androgenic steroids. Of this group testosterone, methyltestosterone and esters thereof are preferred. Representative esters include the propionate, phenylacetate, enanthate and cypionate esters of testosterone and methyltestosterone.

Serum, or total, testosterone or free testosterone determined by analysis of blood or other body fluids will generally refer to natural testosterone. Based on

the above dosages and knowledge of physiological testosterone ranges, one skilled in the art can readily determine what amount of each androgenic steroid or testosterone agent to administer. What is important is that the dosage of the testosterone agent must be sufficient to overcome the deficiency being monitored or treated without administering too great a dosage. However, it is the object of this invention to provide a method of treating testosterone deficiencies to bring the testosterone level in any given female within that female's normal physiological range and the exact dosage is not as critical as is the obtaining of the resultant physiological norm for that patient.

Too high a dosage of testosterone, or application of a dosage for too long a period of time may be manifest by symptoms of testosterone excess, i.e. irritability, clitoral enlargement, increased facial hair and lowering of the voice. By following the guidelines contained in the present invention, such indications will not be manifest and the patient and prescribing physician should not be unduly concerned over undesirable side effects.

Since the genital mucosa readily absorbs androgenic steroids, the initiating of testosterone supplementation in that area quickly provides vitalization of the genitalia as well as providing systemic delivery of testosterone to other areas. As the genital tissues become healthier following topical testosterone application, the blood circulation is improved and testosterone receptors become well supplied with the concomitant increase in sexual sensation and gratification. A sense of well-being and self awareness usually results.

The compounding of a formulation for topical application to the genital mucosa may be in various forms, e.g. a solution, emulsion, cream, gel, ointment, paste and the like. Generally, the concentration of

testosterone or other androgenic steroid will be between about 0.01 and 2.5% by weight of the formulation with concentrations of between about 0.1 and 1.0% being preferred. The carrier used may be a solvent for testosterone or a vehicle in which the testosterone may be uniformly dissolved or suspended.

By "pharmaceutically acceptable carrier" is meant a vehicle or carrier in which the androgenic steroid, and any other ingredients such as enhancers and/or solvents, along with any other additives, are contained in a single or phase separated fluid state. By "fluid" is meant a composition that is not solid but may be present in varying degrees or states of viscosity. The carrier *per se* may serve as a solvent or a solvent or co-solvent may be added. Carriers can be water or organic based and may contain a mixture of liquids or solvents appropriately gelled or thickened. In other words, such carriers may comprise, but are not limited to, solutions, suspensions, emulsions, gels, ointments, creams, pastes or any other similar state which permits the outward diffusion of testosterone or other androgenic steroid and any enhancer, solvent or other additives as desired. The continuous phase forming such carriers can vary from hydrophilic to hydrophobic depending upon the desired combination. Representative inert ingredients other than water include, but are not limited to, polypropylene glycol, polyethylene glycol, polyvinyl alcohols, petrolatum, polyvinylpyrrolidone, mineral oil, silicone oil, ethylene-vinyl acetate polymers or other low molecular weight polymers soluble in water, C_2-C_8 lower alcohols or suitable solvents.

In addition to the carrier, the formulation may contain a solvent (or solvents) and an absorption enhancer (or enhancers). Optionally, the formulation can also comprise preservatives, fragrances and/or stabilizers. Typically, the androgenic steroid is in the form of natural testosterone, methyltestosterone, and

esters thereof such as testosterone or methyltestosterone propionate, cypionate, or enanthate.

Suitable enhancers include those conventionally used in the art. Representative of these are C_8 to C_{18} fatty acids, C_1 to C_8 esters of C_8 to C_{18} fatty acids, C_8 to C_{18} fatty alcohols, sorbate esters and salts, glycerol esters of fatty acids, C_7 to C_{22} fatty acid esters of α-hydroxy acids and mixtures of any of the above. Enhancers may be present in any functional amount and will generally be present in amounts of between about 0.01 and 30% by weight.

Also, certain solvents can serve as both solvents and enhancers. Representative of these are C_2 to C_7 alcohols, C_3 or C_4 diols, ethoxydiglycol, DMSO, DMF, DMA, 1-n-dodecyl-cyclazacycloheptan-2-one, N-methyl-pyrrolidone, N-(2-hydroxyethyl)pyrrolidone and the like. As with enhancers, solvents may be present in any functional amount. Since some solvents may actually function as the carrier vehicle, it is not practical to restrict the amount of solvent to any numerical range except to state that "effective amounts" may be utilized.

Other additives such as thickening agents, gums, fragrances, stabilizers, agents to increase the solubility of androgenic steroids (e.g. cyclodextrins, etc.), and the like can also be incorporated into the formulation.

The absorption enhancer or enhancers render the androgenic steroid more readily available by enabling or enhancing its uptake into genital mucosal cells or the surrounding skin. This facilitates delivery to the genital mucosa or the skin and absorption of the androgenic steroid utilized.

Typically, topical formulations comprise from about 0.01% to about 2.5% testosterone and can comprise any concentration within this range which is appropriate to

produce the desired effects. The lowest concentration that can bring about the desired effects is preferred. In that regard formulations comprising from about 0.05% to about 1% testosterone are preferred.

While the invention encompasses the utilization of testosterone, methyltestosterone and esters thereof it may be beneficial to utilize methyltestosterone when administered concurrently with estrogens or when it is preferred estradiol levels be maintained as low as possible. Methyltestosterone does not tend aromatize *in situ* into estradiol whereas small amounts of testosterone may be converted to estradiol. Use of methyltestosterone is of particular value, for example, in women who develop testosterone deficiency as a result of ovarian failure following chemotherapy for breast cancer and who need to keep their estrogen levels as low as possible. However, while the following examples primarily illustrate the use of methyltestosterone, that is not intended to be a limitation on the invention as other androgenic steroids may also be utilized to bring about the desired results but may need to be monitored more carefully.

In the embodiments exemplified in the following Examples 1-15, a dosage of between 0.25 and 0.5 mg methyltestosterone/0.1 ml transmucosal cream is used. In other words, the concentration of methyltestosterone in the topical preparation is between 0.25 and 0.5% by weight. The concentration most appropriate for a particular woman can be determined empirically (e.g., by varying the concentration and assessing the resulting effects on genital atrophy and sexual sensitivity).

In carrying out the present invention upon determining the presence of one or more symptoms of testosterone deficiency, a formulation comprising an androgenic steroid, such as methyltestosterone, at an appropriate concentration is applied to the genital mucosa in sufficient quantity and for sufficient time,

as the patient is monitored by her physician, to reduce genital atrophy and bring about a reduction in the symptoms of testosterone deficiency. Typically this will vary from about one week to three months and, most typically from about three to nine weeks. Subsequently, to keep testosterone blood levels within physiological ranges, topical genital administration is reduced and supplemented by oral, transdermal or parenteral administration of low doses of the androgenic steroid, such as methyltestosterone, in sufficient quantity to maintain the benefits obtained from the use of the topical genital formulation. Preferably, the oral dose of methyltestosterone is in the range of .1 mg to .8 mg per day and the transdermal dose of testosterone, as noted in U.S. Patent 5,460,820, is in the range of 0.05 to 0.5 mg per day for testosterone.

The transdermal or parenteral dose for methyltestosterone or oral or parenteral dosages testosterone may require minor adjustments. However, it is to be noted that the overall ranges for testosterone and methyltestosterone given above overlap considerably such that a general dosage range of testosterone or methyltestosterone, in any administered form, of from about 0.01 to 1.0 mg/day should be suitable. However, this range may vary for any given androgenic steroid according to its relative potency and bioavailability. Therefore the key to the exact amount is that of functionality. Any androgenic dosage that is equivalent to 0.01 to 1.0 mg/day of testosterone or methyltestosterone should be effective.

As described herein, the formulation of the present invention provides a means by which the health of the genital mucosa and sexual sensitivity of the clitoris and vagina can be improved and other systemic benefits of improved testosterone levels can also be achieved.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

The following compositions described are for topical application to the genitals, particularly the genital mucosa, and to the adjacent skin. The formulation comprises an androgenic steroid suitable for testosterone supplementation as noted above in combination with a pharmaceutically acceptable carrier. More than one androgenic steroid or form of testosterone can be included in a single formulation (e.g., to provide forms which can vary in their availability). Testosterone, methyl testosterone and their esters, as noted above, are preferred androgenic steroid agents.

Commercially available carriers can be used to produce the formulation of the present invention or carriers specifically designed for delivery of testosterone to the genital mucosa or skin can be used. For example, a cream base, such as that available from Professional Compounding Centers of American, Inc. ("PCCA") and referred to as PLO gel or Pluronic Lecithin Organogel can be used. The PCCA base includes: soya granular lecithin; Poloxamar 407, NF: isopropyl palmitate, NF; purified water, USP; alcohol, USP; sorbic acid, NF and potassium sorbate, NF.

Alternatively, a cream base, referred to as "Pharmavan cream" and available from The Apotherecary, (Keene, NH), is used in Examples 1-14 below. Pharmavan cream includes; cetyl alcohol NF (1.0%); stearic acid NF (16.0%); isopropyl myristate (5.0%); polyoxyl 40 stearate NF (1.0%); stearyl alcohol NF (1.0%); potassium sorbate (0.1%) and distilled water (qs 100.0%). The cream base is made by combining the cetyl alcohol NF, stearic acid NF, isopropyl myristate, polyoxyl 40 stearate NF and stearyl alcohol NF and heating the resulting combination to 75°C. The potassium sorbate is dissolved in 75% of the distilled water, heated to 75°C and the xanthene gum is dispersed in this potassium

sorbate/distilled water mixture. The two combinations of components are combined, preferably by adding the potassium sorbate/water/xanthene gum combination to the cetyl alcohol-containing combination. The resulting combination (which contains all of the components described above) is homogenized and mixed at slow speed until it is of uniform consistency and makeup. The pH is adjusted, if needed, to be within a range of 4.0 to 5.5 and, preferably, between pH about 4.5 and about 5.0. Sufficient additional distilled water is added (qs to volume) and mixing is carried out to produce a uniform consistency. The resulting combination is allowed to set up (e.g., for 24 hours or sufficient time to produce a cream of the desired consistency). A methyltestosterone topical cream is produced by combining methyltestosterone, ethoxydiglycol and the Pharmavan cream described above. For example, a methyltestosterone topical cream containing 0.5 mg methyltestosterone/0.1 ml cream can be produced by combining 0.150 gm methyltestosterone, 10.0 ml ethoxydiglycol and Pharmavan cream qs 30.0 ml.

In the method of the present invention, the androgenic steroid-containing formulation is applied topically to the genital mucosa, in an effective quantity (a sufficient quantity to improve the health of the genital mucosa and supply testosterone to local testosterone receptors). Testosterone, such as methyltestosterone, in the formulation is absorbed, resulting in increased systemic levels and attendant benefits (e.g., restoration of vital energy, sexual libido, capacity for orgasm and intensity of orgasm, sensitivity to sexual stimulation in the nipples, improvement of muscle tone, improved moisture in skin and hair, increased deposition of bone, stimulation of red blood cell production and improvements in mood and sense of well-being). The topical formulation is applied one or more times a day for a sufficient number

of days (e.g., 1 week to 3 months and, generally 3-9 weeks) to produce the desired effect. When sufficient benefit has been achieved through topical genital application, topical genital application is reduced or discontinued and oral or transdermal supplementation with an appropriate low dosage of the same or different androgenic steroid is begun, in order to maintain blood levels of testosterone sufficient to maintain the effects achieved as a result of topical application. For example, application to the genital mucosa can be discontinued and a low dose of testosterone can be administered orally, transdermally or parenterally, in an amount sufficient to maintain the desired blood levels. Alternatively, application to the genital mucosa can be continued but at a reduced level or frequency (e.g., using a formulation containing less androgenic steroid than the formulation initially used or applying the formulation on a less frequent basis) in combination with oral, transdermal or parenteral administration of one or more of the forms of testosterone. In general, methyltestosterone will be administered orally at a dose of from about 0.10 mg to about 0.80 mg per day; the dose will be adjusted according to an individual woman's needs. In a particular embodiments of Examples 1-14, the dose will be from about 0.3 mg to about 0.6 mg per day. Methyltestosterone capsules (e.g., capsules containing 0.05 mg, 0.10 mg, 0.25 mg or 0.50 mg methyltestosterone) can be administered. The dose of oral methyltestosterone can be taken in a single daily dose or in two or more smaller quantities.

The following case studies based on a physician determination of testosterone deficiency are exemplary of the results obtained using testosterone supplementation according to the invention. The formulation applied was compounded as described above,

i.e. methyltestosterone, ethyoxydiglycol and Pharmvan cream.

EXAMPLE 1

Patient A is a 41 year old woman who had a hysterectomy three years prior. She had huge fibroid tumors of the uterus weighing up to five pounds. Her ovaries were not removed. She described herself prior to the surgery as a very sexually active woman in a satisfying relationship with a wonderful man. Following her surgery, she lamented that she "feels nothing" sexually. She has noticed some loss of scalp hair but not much change in pubic hair. She complained that she has a loss of general vital energy and is very distressed about lack of sexual feeling, pleasure and libido.

Tests showed that her total serum testosterone was virtually unmeasurable at 3.0 ng/dl (normal range 15-80 ng/dl) and serum free testosterone was also negligible at 0.16 pg/ml (normal range 1.0-2.0 pg/ml). Serum estradiol was within normal limits at 125 pg/ml. Thyroid hormone studies were within normal limits.

Patient A was treated with topical methyltestosterone cream 0.25%, .1 ml applied to the genital mucosa each night after bathing and, after 4 days, she noted an appreciable improvement in genital sexual sensitivity and pleasure on stimulation. After three weeks she stated that her sexual vitality had been restored and that she "feels like herself again."

EXAMPLE 2

Patient B is a 53 year old woman whose menstrual periods stopped three years ago, when she was age 50. She complained of changes in her personality, having rageful feelings, being forgetful, unable to concentrate, having no energy and was most troubled because she had no sexual feelings at all. Her sexual

feelings had been waning somewhat for several years. She reported she last felt fully well and sexually alive when she was about 40. She had previously enjoyed a very good sexual relationship with her husband but now had no sexual interest at all. She stated that she took estrogen for 3-4 months about a year ago but stopped because she got nervous about potential breast cancer risks. On a mammogram, some calcifications showed up, but were negative for cancer on needle biopsy. Patient B complained of having hot flashes and disrupted sleep.

Patient B's total serum testosterone was low at 14.8 ng/dl; as was serum free testosterone, at 0.38 pg/ml. Her serum estradiol was 6.28 pg/ml, which is in the menopausal range. Thyroid hormone levels were within normal limits.

She was started on methyltestosterone topical cream 0.25%, 0.1 ml per day applied to the genital mucosa. After six weeks on this regimen, Patient B was sleeping much better, having fewer hot flashes, more comfortable in mood and with distinctly improved sex drive and capacity for sexual pleasure.

EXAMPLE 3

Patient C is a 39 year old woman complaining of decreases clitoral and vaginal sensitivity, low libido and dyspareunia. For the past year, she also had a depressed mood, and her energy level was quite low. Menarche began at age 13, and her periods had never been regular.

Serum testosterone was low at 14.0 ng/dl, and serum free testosterone was low at .3 pg/ml. Thyroid hormone levels were within normal limits.

She was started on Premarin 0.9 mg q.d., and micronized progesterone 200 mg q.d. for the first ten days of each month to insure that she had proper shedding of her endometrium. After six weeks, she felt somewhat better, but noticed no improvement in her sex

drive. She was started on topical methyltestosterone 0.25%, using .1 ml daily applied to her genital mucosa. At her next visit, six weeks later, she reported that her mood was fine, her energy was good, and her sex drive was markedly improved. She was having no pain on sexual intercourse, and was very pleased with her present state.

EXAMPLE 4

Patient D is a 60 year-old-woman who has never been treated with estrogen, and sought professional advice complaining of the decline in her energy and her sex drive. Her last menstrual flow was at about age 50. She had not had sexual intercourse since she was about age 51. She had vaginal dryness.

On laboratory evaluation, she was found to have an elevated serum FSH of 66.6 MIU/ml, compatible with her menopausal status. Serum estradiol was <20 pg/ml. Serum testosterone was 12 ng/dl. A free testosterone level was .74 pg/ml.

Because of her low serum estradiol level, she was started on Premarin 0.9 mg daily, to be cycled with micronized progesterone 200 mg daily for the first ten days of each month. After 6 weeks she was tolerating this regimen well but having no improvement in sexual energy. She was started on topical methyltestosterone 0.25%, using .1 ml daily applied to her genital mucosa. Six weeks later, she reported increased sexual sensitivity and pleasure, and improved sexual libido.

EXAMPLE 5

Patent E is a 46 year old woman who, at age 38, had a total hysterectomy and bilateral salpingo-oophorectomy for ovarian cyst and severe endometriosis. She was subsequently placed on the Climara patch 0.1 mg. On the estrogen treatment, she developed migraine headaches once weekly which were severe and associated with

vomiting. These were treated with Imitrex 25 mg. She came in complaining of markedly decreased sex drive.

On hormonal evaluation, her serum estradiol was 44 pg/ml, serum total testosterone was low at 10.3 ng/dl, and free testosterone was very low at <.15 pg/ml. DHEA-S was within normal limits for her age at 109 mcg/dl, as were thyroid function studies.

She was started on topical methyltestosterone 0.25%, using .1 ml daily applied to her genital mucosa. Six weeks later, she reported that her libido was better, she was sleeping better and having fewer migraine headaches. Her libido improved further on slight increase in the testosterone to 1.5 ml alternating with 1.0 ml per day.

EXAMPLE 6

Patient F is a 40 year old woman who had a hysterectomy and bilateral salpingo-oophorectomy five years ago for bad menstrual periods, severe endometriosis, and painful intercourse. She had enjoyed an active sex life and had a good sex drive prior to the surgery, although intercourse had been painful due to the endometriosis. Following the surgery, she was placed on Premarin .625 mg per day. During the 2 year period previous to her visit, she had suffered a complete loss of sexual libido and activity. During the previous year, she has had increasing problems with insomnia and frequent headaches. Her weight has increased 30-40 lbs in the past five years, and she was much less active than she had been previously.

A serum estradiol was 186 pg/ml, a total testosterone was low normal at 18 ng/dl, and the free testosterone was the low end of the normal range at 1.05 pg/ml. Thyroid function studies were within normal limits.

The patient was started on methyltestosterone .25% cream, .1 ml applied to the genital mucosa daily. On

her return in 8 weeks, she was pleased to report increased sexual sensitivity and desire, better energy and sleep. She has begun to exercise, and reports improved muscle tone and a weight loss of 4 pounds.

EXAMPLE 7

Patient G is a 41 year old woman who was still menstruating regularly, with periods every 28 days, but who reported loss of sexual libido and was very distressed that she had lost most of her pubic hair. Migraine headaches, which she has had since she was a teenager, had become more problematic. She noted muscle weakness, and had also gained 20-25 pounds and had noted a marked decline in her energy level. She had also been having some problems with concentration.

On hormonal evaluation, she had a slight elevation of her FSH and a serum estradiol of 69.9 pg/ml and 46.2 pg/ml on separate occasions, both somewhat low but not quite menopausal levels. Her serum testosterone was quite low at 1.9 ng/dl, and a free testosterone was low at 0.79 pm/ml.

To stabilize her perimenopausal status, she was started on Premarin 0.9 mg daily, with the subsequent addition of .25% methyltestosterone cream, 0.1 ml applied to the genital mucosa daily. After 8 weeks, she reported improvement in her sexual libido, fewer migraine headaches and better general energy.

EXAMPLE 8

Patient H is a 43 year old woman suffering severe depression and loss of sexual libido and pleasure since a hysterectomy and bilateral salpingo-oophorectomy four years ago for large uterine myomata. She had been treated with a variety of estrogen preparations, including Ogen and Estraderm. She had a trial of an androgen implant at one time to determine if it would be beneficial. She did not notice improvement in mood or

libido and felt agitated (possibly from too high a blood level of testosterone). She had been treated for major depressive disorder with multiple antidepressants including Zoloft, Desyrel, Parnate, Wellbutrin, Anafranil, Prozac, lithium, Ritalin, Risperidone, and ETC.

Serum estradiol was 38.6 pg/ml, total testosterone level was low at 4.9 ng/dl and free testosterone was 0.24 pg/ml. Thyroid hormone levels were within normal limits. Increasing her estradiol by prescribing Estraderm 0.1 mg resulted in some improvement in her depression. Six weeks later, she was started on methyltestosterone topical cream 0.25% at .1 ml applied to the genital mucosa daily. After 6 weeks, the patient reported better energy and improvement in sexual sensitivity and libido.

EXAMPLE 9

Patient I is a 48 year old woman with a history of carcinoma of the breast diagnosed when she was 40 and treated with chemotherapy. The carcinoma was found to be estradiol receptor negative, progesterone positive. Following the chemotherapy, she became menopausal and her libido declined. She also noted a decline in her energy and increase in symptoms of depression. She was taking Zoloft 50 mg daily and was using Estrace vaginal cream once weekly.

Serum estradiol was very low at 29 pg/ml. Interestingly enough, serum and free testosterone levels were within normal limits at 33 ng/dl and 1.7 pg/ml, respectively. Thyroid hormone levels, prolactin and DHEA-S evaluations were within normal limits.

On the chance that her testosterone receptors were deficient because of the low estradiol levels (estrogen stimulates production of testosterone receptors) and that a higher level of testosterone might partially overcome this deficiency, she was given

methyltestosterone cream 0.25%, to use 0.1 ml per day on the genital mucosa. After 6 weeks, she reported a return of sexual sensation and libido and a significant improvement in her mood.

EXAMPLE 10

Patient J is a 50 year old perimenopausal woman who had been taking a contraceptive (Norinyl), containing ethinyl estradiol and norethindrone. Prior to starting the oral contraceptive, she had been experiencing some hot flashes. While taking the oral contraceptive, her sex drive had decreased. She was having painful intercourse, and she had also noted some loss of pubic hair.

Laboratory evaluation showed that she had no measurable total testosterone, and virtually no serum free testosterone (.25 pg/ml).

The oral contraceptive was discontinued and she was placed on Premarin 0.9 mg per day and topical methyltestosterone .25% cream, 0.1 ml per day to be applied to her genital mucosa. Return visit 8 weeks later found her pleased to be enjoying pain-free intercourse, greater sexual pleasure and significant improvement in sexual libido. Return visit in three months found the return of normal amount and texture of pubic hair.

EXAMPLE 11

Patient K is a 55 year old woman who has been on hormone replacement therapy since age 42, when she began suffering from night sweats and vaginal dryness. At the time of consultation, she was using Estraderm 0.05 mg twice weekly. She had had problems with mild depression for many years, but it had been worse since she had been menopausal. She had been taking Prozac 20 mg daily for the past seven years. She had had poor libido for more than 8 years.

Serum estradiol was 47.3 pg/ml, serum total testosterone was less than 20 ng/dl and free testosterone was very low at 0.48 pg/ml. Serum T3, T4, free T4 and TSH levels were within the normal range.

Estraderm dosage was increased to 0.1 mg twice weekly. After 6 weeks, she noted mild improvement in the vaginal dryness, but no improvement in sexual libido or sensitivity. She was started on methyltestosterone 0.25% cream, 0.1 ml per day applied to the genital mucosa. After 6 weeks, she reported improvement in sexual sensitivity and return of libido. She also noted markedly improved vaginal lubrication on intercourse.

EXAMPLE 12

Patient L is a 50 year old woman complaining of low energy, mood problems, and depression. She had been taking Wellbutrin 300 mg daily for the past 3-4 years. Her sex drive was low and she was unable to have an orgasm. Her sexual activity had declined gradually over the past 10 years. When she was younger she enjoyed a very active sex life. She still had slight menstrual periods about every three weeks.

Laboratory values showed an elevated FSH at 33.0 mlU/ml, serum estradiol at 139.0 pg/ml. Serum total testosterone was 27 ng/dl, but free testosterone was very low at 0.34 pg/ml.

She was started on topical methyltestosterone 0.5%, 0.1 ml per day applied to the genital mucosa. After three weeks, she had only a mild increase in libido. Premarin 0.9 mg was added, and within 6 weeks, her sex drive was much better, and her mood was improved.

EXAMPLE 13

Patient M is a 48 year old woman who, two years previous, had a total hysterectomy with bilateral salpingo-oophorectomy because of fibroids. Following

the surgery, she was placed on Premarin 0.625 mg. Complaining of lethargy and depression, the dosage was increased to .9 mg daily. Subsequently, about one year previous, the dosage was decreased to 0.625 mg because of her concerns regarding the risk of breast cancer. Immediately following the surgery, she noted a decrease in her sex drive and sexual function. She is unable to have an orgasm.

On hormonal evaluation, her serum estradiol was 75 pg/ml, serum total testosterone was low at 11.6 ng/dl, and serum free testosterone was virtually absent at 0.2 pg/ml.

The patient was started on methyltestosterone .25% cream 0.1 ml applied daily to the genital mucosa. Returning after 6 weeks, she reported the return of sexual sensitivity, markedly improved sexual libido and capacity for orgasm. She also noted a marked improvement in general energy.

EXAMPLE 14

Patient N is a 57 year old woman who, at age 45, began to notice mood changes and decline in energy. At that time, she was also having the onset of heavy menstrual bleeding, was told that she had myomata and needed a hysterectomy. When she was 47, a bilateral salpingo-oophorectomy and total hysterectomy was performed. Following the surgery, her moods worsened and she had a marked decline in her sex drive. She is unable to have an orgasm. She was sent to a psychiatrist and was treated with tricyclics, Nardil, Zoloft and Prozac, with no significant improvement in her mood or sexual function. For a six month period she was treated with Premarin 0.625 mg daily, which was then increased to 1.25 mg daily. She developed fluid retention, headaches, and continued depression, so she discontinued estrogen therapy. She complained of having

very low energy, insomnia, difficulty falling asleep and early morning awakening.

Laboratory testing revealed serum estradiol of <20 pg/ml, total serum testosterone of 21 ng/ml and serum free testosterone at 0.77 pg/ml. Thyroid function studies were all within normal limits. Serum cholesterol was elevated at 329 mg/dl, and triglycerides were 394 mg/dl.

She was started on Estrace 1.0 mg daily, tolerated it well and it was subsequently increased to 2.0 mg daily. She noted some improvement in mood and general energy, but no improvement in sexual function. She then was given methyltestosterone 0.25% cream, 0.1 ml daily applied to the genital mucosa. On return six weeks later, she felt markedly better, had the return of sexual sensitivity and pleasure, improved libido and capacity for orgasm. Her mood and energy was substantially better.

Example 15

Patient O is a 51 year old woman who had her last menstrual period one year previous. She reported that when she was 47, having irregular menstrual periods with light flow. She experienced a loss of sexual libido and general energy over a period of several months. She noted a significant loss of pubic hair and flaccidity of her labia. Scalp hair was dry and breaking. For the previous 18 months she had been taking Premarin .625 mg. and cycling with Provera 10 mg for ten days each month. She reported a feeling of "flatness" and lack of zest and experienced no sexual sensation in nipples or genitals.

Laboratory tests showed total testosterone below the limits of detection and free testosterone was low at 0.1 pg/ml. She had tried using Estratest H.S. which made her feel agitated and disrupted her sleep.

She was treated with testosterone propionate 2% in petrolatum, a small amount applied to the genital mucosa once per day. After two months, she began to experience sexual sensitivity and pleasure and the return of sexual libido and general vital energy. After four months, her pubic hair had regrown to normal amount and texture. Serum testosterone was elevated significantly above physiological levels at this point. The topical preparation was discontinued in favor of oral methyltestosterone 0.25 mg. per day, which sustained her libido, capacity for sexual pleasure and feeling of well being.

The following examples are representative of various formulations and treatment regimens that illustrate the invention.

Three pharmaceutical carriers are illustrated as representative. Carrier A is the Pharmvan cream carrier given above as used in Examples 1-14. Carrier B is a gelled base comprising ethanol/water/glycerin (50:20:30 volume) gelled with 1.5% w hydroxypropyl cellulose and containing about 2.5% w of an oleic acid ester of glycerol as an enhancer. Carrier C is a petrolatum base containing 2% isopropyl palmitate as an enhancer.

Oral Tablet A is a sugar coated tablet containing the specified amount of methyl testosterone in an inert lactose/magnesium stearate/microcrystalline cellulose carrier. Oral Tablet B is a pressed tablet containing the specified amount of fluoxymesterone in a calcium stearate/corn starch carrier. Injectable solution A is a testosterone cypionate ester uniformly contained in a cottonseed oil/benzyl alcohol solution stabilized by benzyl benzoate. Transdermal patch A is a matrix patch as described in U.S. Patent 5,460,820 formulated to deliver 100 µg/day of testosterone.

Following diagnoses of one or more symptoms of testosterone deficiency in a woman the designated topical formulation is applied one or more times daily

to the genital mucosa for a time sufficient to alleviate the symptoms of testosterone deficiency. When indicated, the topical treatment is replaced by an oral, transdermal or parenteral maintenance formulation administered using the formulation and/or dosage indicated.

Example 16

Topical formulation:	0.2% w. natural testosterone in Carrier B
Maintenance:	Transdermal Patch A

Example 17

Topical formulation:	0.15% w. micronized testosterone propionate in Carrier C
Maintenance:	0.5 mg testosterone cypionate in Injection Solution A administered weekly

Example 18

Topical formulation:	0.3% w. testosterone in Carrier A
Maintenance:	.2 mg fluoxymesterone as Oral Tablet B administered daily

Example 19

Topical formulation:	0.15% w. testosterone enanthate in Carrier C

Example 20

Topical formulation:	0.05% w. testosterone enanthate in Carrier A
Maintenance:	Transdermal Patch A

Example 21

Topical formulation:	0.15% w. dehydroepiandrosterone in Carrier B
Maintenance:	0.1 mg dehydroepiandrosterone as Oral Tablet B administered daily

Example 22

Topical formulation:	0.2% w. testosterone in Carrier C
Maintenance:	.2 mg methyltestosterone as Oral Tablet A administered daily

Example 23

Topical formulation:	0.1% w. methyltestosterone propionate in Carrier A
Maintenance:	Transdermal Patch A

Example 24

Topical formulation:	0.12% 50/50 ratio of testosterone and testosterone propionate in Carrier B
Maintenance:	.2 mg fluoxymesterone as Oral Tablet B administered daily

These examples are intended to be indicative only of regimens that can be utilized. Each regimen will preferably be customized to meet the needs of the patient. While the examples have been directed primarily to the delivery of an androgenic steroid to provide needed supplementation based on determination of a need for such, it is likely that such administration will be concurrent with the administration of estrogen and/or estrogen and progestin formulations.

In addition to the above, it is believed, the supplementation of testosterone by means of genital application of an effective amount of testosterone in a pharmaceutically acceptable carrier may enhance coronary vasodilation, and has effects on carbohydrate metabolism beneficial to blood vessel endothelium. Genital topical application of testosterone to women to bring testosterone levels to within normal limits may have a cardiovascular protective effects.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

1. A formulation for topical application comprising from about 0.01% to about 2.5% of an androgenic steroid uniformly contained in a pharmaceutically acceptable carrier.

2. A formulation according to Claim 1 wherein said pharmaceutically acceptable carrier is a member selected from the group consisting of solutions, suspensions, emulsions, gels, ointments, creams and pastes.

3. A formulation according to Claim 2 additionally containing at least one member selected from the group consisting of enhancers and solvents.

4. A formulation according to Claim 3 containing both an enhancer and a solvent.

5. A formulation according to Claim 4 wherein said solvent is a member selected from the group consisting of C_2 to C_7 alcohols, C_3 or C_4 diols, ethoxydiglycol, DMSO, DMF, DMA, 1-n-dodecyl-cyclazacycloheptan-2-one, N-methyl-pyrrolidone, N-(2-hydroxyethyl)pyrrolidone and mixtures thereof.

6. A formulation according to Claim 5 wherein the enhancer is a member selected from the group consisting of C_8 C_{18} fatty acids, C_1 to C_8 esters of fatty acids, C_8 C_{18} fatty alcohols, sorbate esters and salts, glycerol esters of fatty acids, C_7 to C_{22} fatty acid esters of α-hydroxy acids and mixtures thereof.

7. A formulation according to Claim 5 wherein the androgenic steroid is a member selected from the group consisting of natural testosterone, testosterone esters, methyltestosterone, androstenedione, andrenosterone, dehydroepiandrosterone, fluoxymesterone, methandrostenolone, 17α-methylnortestosterone, norethandrolone, dehydrotestosterone, oxymetholone, stanozolol, ethylestrenol, oxandrolone, bolasterone and mesterolone.

8. A formulation according to Claim 7 wherein the androgenic steroid is a member selected from the group consisting of testosterone, methyltestosterone and esters thereof.

9. A formulation according to Claim 8 wherein the androgenic steroid is methyltestosterone.

10. A formulation according to Claim 8 wherein the androgenic steroid is a member selected from the group consisting of testosterone and testosterone esters.

11. A method of providing an androgenic steroid to a woman in need of testosterone supplementation, comprising topically administering a formulation comprising from about 0.01% to about 2.5% of the androgenic steroid in a pharmaceutically acceptable carrier to the genital mucosa of the woman.

12. A method according to Claim 11 wherein said pharmaceutically acceptable carrier is a member selected from the group consisting of solutions, suspensions, emulsions, gels, ointments, creams and pastes.

13. A method according to Claim 12 wherein the androgenic steroid is a member selected from the group consisting of natural testosterone, testosterone esters, methyltestosterone, androstenedione, andrenosterone, dehydroepiandrosterone, fluoxymesterone, methandrostenolone, 17α-methylnortestosterone, norethandrolone, dehydrotestosterone, oxymetholone, stanozolol, ethylestrenol, oxandrolone, bolasterone and mesterolone.

14. A method according to Claim 13 wherein the androgenic steroid is a member selected from the group consisting of testosterone, methyltestosterone and esters thereof.

15. A method according to Claim 14 wherein the androgenic steroid is methyltestosterone.

16. A method according to Claim 14 wherein the androgenic steroid is a member selected from the group consisting of testosterone and testosterone esters.

17. A method of reducing genital atrophy in a woman, comprising applying to the genital mucosa of the woman a formulation comprising from about 0.01% to about 2.5% of an androgenic steroid in a cream base.

18. A method according to Claim 17 wherein the androgenic steroid is methyltestosterone.

19. A method according to Claim 18 wherein methyltestosterone is present at a concentration of from about 0.1% to about 0.25%.

20. A method for improving the cardiovascular health of a woman comprising topically administering a formulation comprising from about 0.01% to about 2.5% of an androgenic steroid in a pharmaceutically acceptable carrier to the genital mucosa of the woman.

21. A method of providing an androgenic steroid to a woman in need of testosterone supplementation, which comprises the steps of:

(1) determining the need for testosterone supplementation in said woman as evidenced by the monitoring by a health care professional of one more parameters selected from the group consisting of

(a) serum testosterone levels,
(b) serum free testosterone unbound to globulin
(c) loss of sexual desire,
(d) decreased sensitivity to sexual stimulation of the breasts and genitalia,
(e) decreased ability to achieve orgasm
(f) diminished vital energy and sense of well-being,
(g) loss of muscle tone,
(h) thinning or loss of pubic hair,
(i) genital atrophy not responsive to estrogen supplementation,
(j) presence of dry skin and dry and brittle scalp hair;

(2) providing a composition for topical application containing an effective amount of an

androgenic steroid uniformly contained in a pharmaceutically acceptable carrier, and

(3) topically administering to the genital mucosa of said woman an effective amount of said composition for a period of time sufficient return one or more of the monitored parameters to its desired physiological state.

22. A method according to Claim 21 wherein a monitored parameter is the serum testosterone level.

23. A method according to Claim 22 wherein said desired physiological state is a serum testosterone level of between 15 and 80 ng/dl.

24. A method according to Claim 21 wherein a monitored parameter is the serum free testosterone unbound to globulin.

25. A method according to Claim 24 wherein said desired physiological state is a free testosterone unbound to globulin of between 0.7 and 2.0 pg/ml.

26. A method according to Claim 21 wherein the androgenic steroid is a member selected from the group consisting of natural testosterone, testosterone esters, methyltestosterone, androstenedione, andrenosterone, dehydroepiandrosterone, fluoxymesterone, methandrostenolone, 17α-methylnortestosterone, norethandrolone, dehydrotestosterone, oxymetholone, stanozolol, ethylestrenol, oxandrolone, bolasterone and mesterolone.

27. A method according to Claim 26 wherein the androgenic steroid is a member selected from the group consisting of testosterone, methyltestosterone and esters thereof.

28. A method according to Claim 27 wherein the androgenic steroid is methyltestosterone.

29. A method according to Claim 27 wherein the androgenic steroid is a member selected from the group consisting of testosterone and testosterone esters.

30. A method according to Claim 29 wherein the androgenic steroid is testosterone.

31. A method of progressively providing an androgenic steroid to a woman in need of testosterone supplementation, which comprises the steps of:

(1) topically administering to the genital mucosa of said woman a composition comprising an effective amount of a an androgenic steroid uniformly contained in a pharmaceutically acceptable carrier for a period of time sufficient to provide a testosterone level suitable to the needs of the woman;

(2) discontinuing said topical genital administration; and

(3) orally, transdermally or parenterally administering to said woman an effective amount of an androgenic steroid sufficient to maintain said testosterone level.

32. A method according to Claim 31 wherein said testosterone level is the serum testosterone level.

33. A method according to Claim 32 wherein said serum testosterone level is between 15 and 80 ng/dl.

34. A method according to Claim 31 wherein said testosterone level is serum free testosterone unbound to globulin.

35. A method according to Claim 33 wherein said serum free testosterone unbound to globulin is between 0.7 and 2.0 pg/ml.

36. A method according to Claim 31 wherein the androgenic steroid is a member selected from the group consisting of natural testosterone, testosterone esters, methyltestosterone, androstenedione, andrenosterone, dehydroepiandrosterone, fluoxymesterone, methandrostenolone, 17α-methylnortestosterone, norethandrolone, dehydrotestosterone, oxymetholone, stanozolol, ethylestrenol, oxandrolone, bolasterone and mesterolone.

37. A method according to Claim 36 wherein the androgenic steroid is a member selected from the group consisting of testosterone, methyltestosterone and esters thereof.

38. A method according to Claim 37 wherein the androgenic steroid is methyltestosterone.

39. A method according to Claim 37 wherein the androgenic steroid is a member selected from the group consisting of testosterone and testosterone esters.

40. A method according to Claim 39 wherein the androgenic steroid is testosterone.

41. A method according to Claim 36 wherein the androgenic steroid in step (1) is present in said carrier for topical application at a concentration of between about 0.01 and 2.5% and is administered in step (3) as a dosage of between about 0.25 and 0.8 mg/day.

42. A method according to Claim 41 wherein the androgenic steroid is methyltestosterone.

43. A method according to Claim 42 wherein the carrier for topical application is a cream.

44. A method according to Claim 43 wherein the methyltestosterone dosage in step (3) is administered orally.

45. A method according to Claim 41 wherein the androgenic steroid is testosterone or an ester thereof.

46. A method according to Claim 45 wherein the dosage in step (3) is administered parenterally.

47. A method according to Claim 45 wherein the dosage in step (3) is administered transdermally.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/02089

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/56
US CL :514/178
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/178

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- A	US 4,496,556 A (ORENTREICH) 29 January 1985, see columns 5-6, Examples 1-4.	1-7 ----- 9-47
Y -- A	US 4,863,970 A (PATEL et al.) 05 September 1989, see column 5, lines 20-30, column 9, lines 49-51 and column 18, lines 6-10.	1-10 ------ 11-47

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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